CURRENT LITERATURE

MORTALITY IN EPILEPSY

Mortality in Epilepsy in the First 11 to 14 Years after Diagnosis: Multivariate Analysis of a Long-term, Prospective, Population-Based Cohort

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The United Kingdom National General Practice Study of Epilepsy is a prospective, population-based study of newly diagnosed epilepsy. A cohort of 792 patients has now been followed for up to 14 years (median follow-up [25th, 75th percentiles] 11.8 years, range 10.6-11.7 years), a total of 11,400 person-years. These data are sufficient for a detailed analysis of mortality in this early phase of epilepsy. Over 70% of patients in this cohort have developed lasting remission from seizures, although the mortality rate in the long term was still twice that of the general population. The standardized mortality ratio (SMR), the number of observed deaths per number of expected deaths, was 2.1 (95% confidence interval [CI] = 1.8, 2.4). Patients with acute symptomatic epilepsy (SMR 3.0; 95% CI = 2.0, 4.3), remote symptomatic epilepsy (SMR 3.7; 95% CI = 2.9, 4.6), and epilepsy due to congenital neurological deficits (SMR 25; 95% CI = 5.1, 73.1) had significantly increased long-term mortality rates, whereas patients with idiopathic epilepsy did not (SMR 1.3; 95% CI = 0.9, 1.9). This increase in mortality rate was noted particularly in the first few years after diagnosis. Multivariate Cox regression and time-dependent covariate analyses were utilized for the first time in a prospective study of mortality in epilepsy. The former showed that patients with generalized tonic-clonic seizures had an increased risk of mortality. The hazard ratio (HR), or risk of mortality in a particular group with a particular risk factor compared to another group without that particular risk factor, was 6.2 (95% CI = 1.4, 27.7; $p = 0.049$). Cerebrovascular disease (HR 2.4; 95% CI = 1.7, 3.4; $p < 0.0001$), central nervous system tumor (HR 12.0; 95% CI = 7.9, 18.2; $p < 0.0001$), alcohol (HR 2.9; 95% CI = 1.5, 5.7; $p = 0.004$), and congenital neurological deficits (HR 10.9; 95% CI = 3.2, 36.1; $p = 0.003$) as causes for epilepsy and older age at index seizure (HR 1.9; 95% CI = 1.7,2.0; $p < 0.0001$) were also associated with significantly increased mortality rates. These hazard ratios suggest that epilepsy due to congenital neurological deficits may carry almost the same risk of mortality as epilepsy due to central nervous system tumors and that epileptic seizures subsequent to alcohol abuse may carry almost the same risk of mortality as epilepsy due to cerebrovascular disease. The occurrence of one or more seizures before the index seizure (the seizure that led to the diagnosis of epilepsy and enrolment in the study) was associated with a significantly reduced mortality rate (HR 0.57; 95% CI = 0.42, 0.76; $p = 0.00001$). Time-dependent covariate analysis was used to examine the influence of ongoing factors, such as seizure recurrence, remission, and antiepileptic drug use, on mortality rates in the cohort. Seizure recurrence (HR 1.30; 95% CI = 0.84, 2.01) and antiepileptic drug treatment (HR 0.97; 95% CI = 0.67, 1.38) did not influence mortality rate. There were only 5 epilepsy-related deaths (1 each of sudden unexpected death in epilepsy, status epilepticus, burns, drowning, and cervical fracture), suggesting that death directly due to epileptic seizures is uncommon in a population-based cohort with epilepsy.

Incidence and Risk Factors in Sudden Unexpected Death in Epilepsy: A Prospective Cohort Study

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OBJECTIVE: To determine incidence of and risk factors for sudden unexpected death in epilepsy (SUDEP).
METHODS: Three epilepsy centers enrolled 4,578 patients and prospectively followed these patients for

16,463 patient-years. The cohort was screened for death annually. Deaths were investigated to determine whether SUDEP occurred. Potential risk factors were compared in SUDEP cases and in controls enrolled contemporaneously at the same center.
RESULTS: Incidence of SUDEP was 1.21/1,000 patient-years and was higher among women (1.45/1,000) than men (0.98/1,000). SUDEP accounted for 18% of all deaths. Occurrence of tonic-clonic seizures, treatment with more than two anticonvulsant medications, and full-scale IQ less than 70 were independent risk factors for SUDEP. The number of tonic-clonic seizures was a risk factor only in women. The presence of cerebral structural lesions and use of psychotropic drugs at the last visit were not risk factors for SUDEP in this cohort. Subtherapeutic anticonvulsant levels at the last visit were equally common in the two groups. No particular anticonvulsant appeared to be associated with SUDEP.
CONCLUSIONS: These results support the idea that tonic-clonic seizures are an important proximate cause of SUDEP. This information creates a risk profile for SUDEP that may help direct preventative efforts.

COMMENTARY

Relative to the general population, mortality in people with epilepsy has long been known to be elevated. Only a very small part of this increase is due to sudden unexplained death (SUDEP). Lhatoo et al. presented an updated and highly detailed analysis of mortality and its causes in the well-documented National General Practitioner Study of Epilepsy (NGPSE) after a median of nearly 12 years of follow-up.

Of particular note in this article is the careful detailed three-level analyses that 1) addresses the increase in mortality compared to the population; 2) identifies within the cohort of people with epilepsy, the predictors of mortality as assessed at baseline; and 3) by employing time-dependent covariates in a Cox regression model, incorporates information about seizure recurrence and use of AEDs throughout follow-up.

The results of this study from the UK are highly consistent with and confirm findings from studies in the US (1), Iceland (2), Sweden (3), France (4), and The Netherlands (5). Common points established from these countries are:

a) The overall standardized mortality ratio (SMR) ranges between 1.6 and 4.1. However, in studies that examine this issue, the SMR is greater in remote symptomatic epilepsy (ranging from 2.3 to 6.5), whereas the SMR is not as elevated in cryptogenic/idiopathic epilepsy (ranging from 1.3 to 1.8).

b) The impact of epilepsy appears to be greatest earlier in the course of the seizure disorder and attenuates over time. Lhatoo et al. examined risk during the first and last 7 years of follow-up. Others have taken different time points. Generally, excess mortality is concentrated in the early years after diagnosis.

c) The relative impact, as measured by the SMR, appears greater in younger individuals, under 60, and was lesser in older individuals where the force of mortality (i.e. the population death rate) is greater.

d) Death was increased for many different causes, not all directly related to the individual's epilepsy.

Within the NGPSE cohort and after adjustment for age, risk factors for mortality were primarily related to the underlying cause of the epilepsy, cerebrovascular disease, alcohol, tumor, and congenital neurological deficit. Evidence suggested that generalized tonic clonic seizures were associated with an increased risk of death. This and the finding for congenital neurologic deficits echo the findings of a recent study of SUDEP (6), even though this was not the specific outcome studied by Lhatoo et al. The results for congenital neurological deficits have also been reported for overall mortality in Rochester (1) and Sweden (3).

Finally, the authors performed a highly innovative analysis to determine the effects over time of the occurrence of seizures and the use of AEDs on mortality. No influence was found for any of these, which is perhaps surprising; however, as the authors carefully pointed out, SUDEP is not a major cause of death in this essentially population-based study (N = 1 death only), and these factors might be thought to play their greatest role in SUDEP.

A few minor caveats to consider in interpreting the results include the diagnosis of SUDEP. This has been previously discussed in general and in the United Kingdom specifically by some of the study's authors. It is clearly a diagnosis that may be frequently missed by the usual death certification process. Also, the terminology used in this report is consistent with older studies and differs somewhat from that recommended by the ILAE; thus, when the authors refer to idiopathic, they mean anything that is "not symptomatic." Finally, acute symptomatic and single seizures were classified as epilepsy.

In all, this is the single most detailed account of a large population-based study of mortality in epilepsy and provides valuable information regarding the relative risks and the predictors of mortality in people with epilepsy.

SUDEP is well recognized if not a well understood cause of death in people with epilepsy. The incidence of SUDEP in community and population-based studies varies only slightly across reports and is generally under 1/1000 per year and is as

low as 0.35/1000 per year. By contrast, in studies of special epilepsy cohorts (surgical candidates, people in new drug trials, VNS recipients, etc), the incidence is more on the order of 2-6/1000.

Understanding the causes of SUDEP and developing effective interventions first requires identifying which individuals are at highest risk. Risk factors for SUDEP have been the subject of only a few well-designed studies to date. Walczak et al. presented the results of the most recent of those studies. Participants (N = 4578) at three large epilepsy centers in the Midwest were prospectively enrolled and followed for a total of 16,463 person years. Twenty cases of definite or probable SUDEP were observed during that time. This yielded an incidence of 1.21/1000 per year. Although this is not quite a "population- or community-based" cohort, neither is it a highly skewed cohort of refractory patients. The authors constructed a nested case-control study within their prospective cohort to study potential risk factors for SUDEP. The authors isolated generalized tonic clonic seizures (GTCSs) as the most important seizure-related correlated of SUDEP. Whereas a previous study had identified seizure frequency as important, Walczak et al. demonstrated that, after adjustment for GTCSs, seizure frequency per se was no longer associated with SUDEP. As in the other two previous studies (7,8), polytherapy was associated with an almost four-fold risk of SUDEP independently of the occurrence of GTCS. Finally, the presence of mental retardation (also found in the Canadian study) (7) was independently associated with SUDEP.

Notable strengths of this study include the prospective nature of the study, the very careful and detailed approach to determining the diagnosis of SUDEP, and the careful prospective characterization of the clinical characteristics of the cohort. It is the nature of the beast in studying rare outcomes such as SUDEP that even in large studies, it is difficult to amass a sizable number of cases with the outcome. For this reason, it is imperative that such studies are done in such a way as to allow comparison with other studies of the same subject. The thoughtful approach to selection and analysis of risk factors explicitly addressed the findings of previous studies and allowed meaningful comparison and integration of results of previous reports. The discussion provided a helpful consideration of the significance and clinical implications of the findings. In addition to confirming the importance of polytherapy in SUDEP, this study has pin-pointed GTCS as most likely being the key seizure-related parameter in the occurrence of SUDEP and provided important evidence for the potential increased risk of SUDEP in individuals with mental retardation.

by Anne Berg, Ph.D.

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